The changes to the claims are merely to correct obvious format errors, and do not involve an issue of new matter. Accordingly, applicants respectfully request entry of these changes.

On page 2 of the December 13, 1993 Office Action, the Examiner objected to the specification under 35 U.S.C. §112, first paragraph, as allegedly failing to adequately teach how to make and/or use the invention, i.e. allegedly failing to make an enabling disclosure.

The Examiner maintained that the disclosed utilities of the method in regards to in vivo treatment and/or prevention of HIV infection are not believable in view of contemporary knowledge of the art. The Examiner further maintained that under 35 U.S.C. §132, applicants are required either to (1) submit appropriate proofs in compliance with 35 U.S.C. §101 and §112 to substantiate this alleged utility, or (2) cancel all disclosure of the in vivo anti-HIV utility from the specification. The Examiner maintained that the current specification provides enablement only for the production of the peptides of the invention and their use in vitro. The Examiner also maintained that no evidence of in vivo utility is presented, nor has the applicability of the in vitro test results to the use of the claimed protein in vivo been established.

In response, applicants respectfully traverse the Examiner's objection. Applicants point out that there is no per se requirement for in vivo data in order to establish the in vivo utility of a compound. Specifically, M.P.E.P. §608.01(p) states that "[i]f the asserted utility of a compound is believable on its face . . . , then the burden is upon the Examiner to give adequate support for [objections] for lack of utility . . ." In the subject application, in vitro data are provided showing the ability of CD4-

gamma2 to inhibit HIV binding to, and infection of, CD4-positive cells. Such data are found, for example, at page 16, lines 14-32, and Figures 9 and 10. Applicants maintain that in light of these data, applicants' disclosed in vivo utility of the claimed immunoconjugates in treating and preventing HIV infection is believable on its face. The burden is thus upon the Examiner to give adequate support for her objection for lack of utility. Accordingly, applicants maintain that the specification is enabling and satisfies the requirements of 35 U.S.C. §112, first paragraph.

The Examiner also rejected claims 31 and 39 under 35 U.S.C. §101 for the reasons stated above.

In response, applicants traverse for the reasons put forth supra in connection with the traversal of the objection to the specification under 35 U.S.C. §112, first paragraph.

The Examiner maintained that the enablement of the specification is not commensurate in scope with claims to CD4-Ig chimeric proteins linked to toxins of any sort. The Examiner specifically maintained that although the ordinary artisan would know how to make such toxin conjugates, the only demonstrated method of using the instant peptides is as diagnostic reagents, and toxin conjugates are not generally considered to be useful diagnostic reagents.

In response, applicants traverse for the reasons put forth supra in connection with the traversal of the objection to the specification under 35 U.S.C. §112, first paragraph. Applicants further point out that toxin conjugates are used as therapeutic agents, and not diagnostic agents. Nevertheless, applicants maintain that the stated utility of the claimed toxin conjugates is believable in view of the specification.

The Examiner stated that the deposit of biological organisms is not necessary for enablement of the invention as claimed. The Examiner acknowledges the deposit of organisms under ATCC Accession Numbers 40949-52 and 75192-94 under the terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, the Examiner stated that in the event that the claims are amended such as to necessitate a biological deposit, applicants would be required to state that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in order to be fully compliant with the requirement.

In response, applicants will make a statement concerning restrictions on availability in the event such statement is deemed necessary.

The Examiner further rejected claims 31-33 and 39-41 under 35 U.S.C. §112, first paragraph, for the reasons set forth in the objection to the specification.

In response, applicants traverse for the reasons put forth supra in connection with the traversal of the objection to the specification under 35 U.S.C. §112, first paragraph.

The Examiner further rejected claims 32, 33, 36, 37 and 39-43 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, the Examiner maintained that claims 36 and 37 are indefinite and incomplete, in that it is not clear how many of the

specified chains are comprised by the heterotetramer, nor what the other components of the heterotetramer are.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants have hereinabove canceled claims 36 and 37 without prejudice to applicants' right to pursue the subject matter of these claims in a later filed divisional application. Accordingly, the rejection of claims 36 and 37 is moot.

The Examiner also maintained that claims 32, 33, 40 and 41 are incomplete for failing to recite more than a single agent as comprising the composition. The Examiner noted that a fused CD4-Ig molecule which is further linked to a toxin is still only a single agent, albeit more complex in nature. The Examiner suggested amending the preamble of such claims to delete the reference to a composition, or alternatively, amending the claims to recite additional agents.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants have hereinabove amended claims 32, 33, 40 and 41 to replace the term "composition" with terms which more accurately describe the claimed immunoconjugates. Applicants maintain that the amendment of claims 32, 33, 40 and 41 overcomes the stated grounds of rejection.

The Examiner further rejected claims 30-43 under 35 U.S.C. §103 as allegedly obvious over U.S. Patent Number 5,116,964 (hereinafter '964 patent) either alone or taken with applicants' alleged admissions in the specification of the state of the prior art.

The Examiner maintained that the '964 patent relates to immunoglobulin fusion proteins which comprise immunoglobulin

constant regions fused to "ligand binding partners", which may include the CD4 binding region (citing column 5 of the '964 patent). The Examiner noted that column 5, lines 55-60, states that the fusions of the invention may be further modified by linkage through peptidyl or in vitro generated bonds to additional moieties such as toxins, labels or other groups. The Examiner stated that embodiments include hetero- or homo-multimers, particularly dimers and tetramers. The Examiner further stated that suitable immunoglobulin combining sites and fusion partners are obtained from IgG-1, -2, -3, or -4, IgA, IgE, IgD or IgM. The Examiner stated that the preferred embodiments specified at the first paragraph of column 15 include either the entire heavy chain constant region of the immunoglobulin, or "a sequence beginning in the hinge region just upstream of the papain cleavage site . . ." The Examiner maintained that both these preferred embodiments preserve the disulfide bond region of the hinge region, as specified in the subject specification at page 10. The Examiner further noted that the '964 patent states that the polypeptides of the invention are useful as cell surface adhesion molecules and ligands, and are useful in therapeutic or diagnostic compositions and methods.

The Examiner stated that the particular peptides claimed in the subject application are not specifically disclosed in the '964 patent. However, the Examiner maintained that one of ordinary skill in the art would find it obvious to follow the alleged teachings and motivations therein to construct the claimed CD4-Ig conjugates. The Examiner further maintained that one of ordinary skill in the art would also have found it obvious to attach the chimeric protein to toxins or labels as further suggested by the '964 patent in order to use the chimeric protein as a cytotoxic or diagnostic reagent, respectively, in view of the art-recognized

utility of such reagents as evidenced by the '964 patent.

The Examiner stated that applicants make the following admissions of record in the specification. At page 8, applicants admit that the prior art teaches that anti-HIV antibodies are capable of enhancing infection of monocyte/macrophage cells, presumably by cross-bridging HIV and Fc receptors, and further admit that the prior art teaches that two of the three known Fc receptors have no affinity for IgG2, and the third (FcRII) has only low affinity for IgG2. The Examiner thus maintained that it would have been obvious to one of ordinary skill in the art when constructing CD4-Ig fusions to fuse the CD4-binding domain to IgG2 to lessen the potential for enhancing, rather than inhibiting, infectivity of the HIV virus.

In response, applicants respectfully traverse the Examiner's rejection. Applicants maintain that the '964 patent actually teaches against the subject immunoconjugates. Specifically, column 7, second paragraph of the Detailed Description of the '964 patent expressly excludes CD4 as a possible ligand binding partner. One of ordinary skill in the art would therefore have been taught against the subject immunoconjugates by the '964 patent. Accordingly, applicants maintain that the subject immunoconjugates would not have been obvious to one of ordinary skill in the art over the '964 patent, and that thus, claims 30-35 and 38-43 satisfy the requirements of 35 U.S.C. §103. Applicants again point out that claims 36 and 37 have been canceled hereinabove, and that the Examiner's rejection is thus moot with respect to these claims.

Finally, the Examiner rejected claims 30-43 under 35 U.S.C. §103 as allegedly unpatentable over International Publication No. WO 89/02922 (hereinafter '922) in view of Capon, et al. (Nature).

The Examiner stated that WO 89/02922 discloses CD4-Immunoglobulin adhesions, which comprise the gp120-binding domain of CD4 fused to various immunoglobulin constant regions. The Examiner noted that the paragraph on page 10 states "[i]t is preferable that the V1V2 or V1-4 (of CD4) be fused at their C-termini to the immunoglobulin constant region. The precise site at which the fusion is made is not critical . . ." The Examiner further noted that at the top of the next page, particular species comprising the first 180 amino acids of CD4 are disclosed, linked to the kappa or IgG1 heavy chain constant region. The Examiner stated that the paragraph bridging pages 11-12 states that "[a]ccording to this invention, CD4-IgG immunoadheson chimeras are readily secreted wherein the CD4 epitope is present in heavy chain dimers, light chain monomers or dimers, and heavy and light chain heterotetramers." The Examiner noted that the first full paragraph of page 13 states suitable fusion partners to include IgG-1, -2, -3 or -4, IgA, IgE, IgD, or IgM. The Examiner further noted that the paragraph bridging pages 15-16 discloses fusions which further comprise an adhesion conjugated with a toxin. The Examiner also noted that pharmaceutical compositions are disclosed at page 27, first full paragraph. The Examiner stated that WO 89/02922 does not specifically disclose tripartite chimeras combining CD4, Ig and toxin or marker moieties.

The Examiner pointed out that Capon et al., in their article on designing CD4 immunoadhesons for AIDS therapy, disclose that one can increase the stability of a rapidly cleared molecule (e.g. CD4) by fusing it to a long lived molecule, such as an immunoglobulin, or the Fc fragment thereof.

The Examiner maintained that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to construct a chimeric protein comprising CD4 and a toxin

or marker as disclosed by '922, and further comprising an immunoglobulin constant region in view of the teaching by Capon et al. that such would be expected to increase the half-life of the chimeric molecule, because of the art-recognized utility of generating a more stable species. The Examiner maintained that one of ordinary skill in the art would further have found it obvious to attach the chimeric protein to toxins or labels as further suggested by '922 in order to use the chimeric protein as a cytotoxic or diagnostic reagent, respectively, in view of the art-recognized utility of such reagents.

In response, applicants respectfully traverse the Examiner's rejection. Applicants maintain that the heterotetramers of the subject invention would not have been obvious to one of ordinary skill in the art over '922 and Capon, et al., and that thus, claims 30-35 and 38-43 satisfy the requirements of 35 U.S.C. §103. Applicants also maintain that the homodimers of the subject invention would not have been obvious over '922 and Capon, et al. Specifically, applicants point out that the subject homodimers differ from the proteins of '922 in that the subject homodimers possess both the entire hinge domain of an IgG2 moiety as well as the remaining portion of the IgG2 moiety. The entire hinge domain is important both for the proper dimerization and biological function of the homodimers as discussed at pages 10 and 11 of the subject specification. The IgG2 moiety is also important for the biological function of the homodimers, since IgG2 binds only to the FcRII receptor, and only weakly at that. The binding properties of IgG2 render it advantageous over other IgG moieties with respect to lessening the potential both for enhancing the infectivity of HIV in an infected subject and for increasing the likelihood of transmitting HIV from infected mother to newborn. The advantages of the entire hinge domain and IgG2 moiety of the subject

homodimers are neither taught nor suggested by '922 and Capon, et al. Moreover, applicants point out that neither '922 nor Capon, et al. teach or suggest toxin-linked immunoconjugates. One skilled in the art therefore would not have known to make the subject toxin-linked immunoconjugates in view of '922 and Capon, et al. Accordingly, applicants maintain that the subject immunoconjugates would not have been obvious to one of ordinary skill in the art over '922 in view of Capon, et al., and that thus, claims 30-35 and 38-43 satisfy the requirements of 35 U.S.C. §103. Applicants again point out that claims 36 and 37 have been canceled hereinabove, and that the Examiner's rejection is thus moot with respect to these claims.

In view of the preceding discussion, applicants respectfully request that the Examiner reconsider and withdraw the objections and rejections made in the December 13, 1993 Office Action.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $420.00 extension fee, is deemed necessary in connection with the filing of this Amendment. If any additional

fee is required, authorization is hereby given to charge the amount of any such additional fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

6/13/94

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